



Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

January 14<sup>th</sup>, 2004

**Docket 2003D-0497**

**FDA Guidance Document on Pharmacogenomics Data Submissions**

Dear Sir/Madam,

Attached you will find comments from Johnson and Johnson pharmaceutical business and research organizations regarding the Draft Guidance for Pharmacogenomic (PGx) Data Submission, published in the Federal Register November 3, 2003.

If you have any questions or concerns regarding the attachment, please feel free to contact me. We appreciate the opportunity to comment as a company and look forward to hearing from the Agency in the near future.

A hard copy of this electronic submission is forthcoming. Please confirm receipt of this electronic correspondence for our records.

Sincerely yours,

A handwritten signature in cursive script that reads "Iman Barilero".

Iman Barilero, PhD, PharmD  
Associate Director, European Regulatory Affairs  
Global Regulatory Affairs and Quality Assurance  
Johnson & Johnson Pharmaceutical Research and Development

Attachment (1)

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**Johnson and Johnson (J&J) RESPONSE TO PROPOSED FDA GUIDANCE  
DOCUMENT ON PHARMACOGENOMICS DATA SUBMISSIONS**

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## **I. INTRODUCTION**

J&J welcomes the opportunity to offer comments on the Draft Guidance for Pharmacogenomic (PGx) Data Submission. Our comments were gathered from several J&J companies engaged in pharmaceutical R&D, molecular diagnostics and pharmacogenomics research, namely: J&J Pharmaceutical Research and Development, LLC; Veridex, LLC; ALZA Corporation; Centocor, Inc.; Ortho Clinical Diagnostics, Inc.; Tibotec, Inc.; and SCIOS, Inc.

We certainly support the FDA's position on the promises of PGx to improve the drug development process and to benefit the public. The interest and encouragement displayed by the FDA to use genomic approaches in drug development are welcome and timely. We are proactively preparing to implement processes to be in alignment with the FDA's goals.

Integration of PGx in drug development provides the links between different phases of development. It is essential that the meaning and interpretation of PGx information are clear and consistent between industry and the FDA to avoid the unintended reciprocal effect of delaying the clinical development and review processes. Although not a new field, PGx is evolving and is still in an early stage of development. Industry will play a key role in the scientific progress of this field. It will be crucial to work together with regulators to transpose the science into practical regulations to ultimately improve public health.

## **II. GENERAL EXECUTIVE COMMENTS**

We believe that several areas within the guidance require reevaluation or clarification. The general areas raising questions are described in this section followed by specific comments, examples and recommendations for consideration by the FDA in later sections.

### **Biomarker Status**

The structure of the draft guidance is based, in part, on the regulatory requirements of three categories of data. Thus it becomes of critical importance to determine exactly what criteria delineate the categories. Additionally, biomarkers may make the transition from one category to another during the course of the development of a compound, increasing the need for clear definitions. The following questions were recurrently raised during our review: For a given biomarker, what impact would a change in biomarker status have on data submission requirements? What are the boundaries among "Known Valid Biomarkers", "Probable Valid Biomarkers" and "Non-Valid Biomarkers (exploratory, VGDS)"? Who is responsible for the validation of biomarkers? There is a clear need for improved definitions of boundaries between the categories of data".



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#### **Use of PGx Data (VGDS and Decision Making)**

**VGDS:** It is in industry's best interest to support the voluntary submission of PGx data to the FDA and to collaborate, in a real time manner, as to the use of these data to support the timely development and delivery of medicines to patients. Industry is open to disclosing these data to the FDA, however, the details on the use of these data need to be clarified in order to encourage voluntary submission and to ensure the efficient development of drugs. If it is perceived by industry that the submission and review, although collaborative, are resource-constraining and can ultimately negatively impact the progress of drugs to market, industry may be more reluctant to volunteer the submission of these data.

We agree that it is societal obligation to inform the FDA on the findings of pharmacogenomic research in industry. The FDA has stated that notification of IND and NDA holders will be done through public or confidential process, as appropriate. The FDA will use defined processes, including a proposed Interdisciplinary Pharmacogenetics Review Group (IPRG), to make the determination. It is felt that transparency is needed to elaborate on the process by which the FDA will use voluntary submissions (VGDS) from multiple companies to make a regulatory decisions. The Draft Guidance proposes the IPRG that would review all voluntary data submissions. The Guidance also makes assurances that data from the VGDS will not affect the regulatory approval process of a compound for which voluntary submissions were made. One can conceive of members of the IPRG participating in the review of NDA applications who will have also seen relevant voluntary submissions from multiple companies. It is difficult to imagine that perceived patterns and trends from the voluntary data would not influence an individual's view of the compound's status during review of the NDA. We would suggest that members of the IPRG not be directly involved in regulatory decision making for a compound. Clarification is required on how the FDA will use the data from VGDS as well as on the responsibility and constituency of the IPRG.

**Decision Making:** It is important that PGx data are not interpreted in isolation but rather be considered in the context of other biological data, and that the differences between the clinical pharmacogenomics applications and the pre-clinical toxicogenomic applications be distinguished. There is some concern that unbalanced weight may be placed on the genomic data. For example, such data may be used to reject compounds if there are equivocal results from a conventional validated assay. The current Draft Guidance may also inadvertently instill exaggerated caution over engagement in PGx activities by implying that data from accumulated submissions may reveal new interpretations relevant to safety evaluation that individual companies may miss. We recommend that greater detail be included on how PGx data will be used in decision making.



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### **Case Scenarios**

The concept of hypothetical cases in the document is very useful but requires more thorough descriptions. A dialogue with the pharmaceutical industry would help in establishing clearer and more realistic examples.

### **Communication Back to Industry**

We encourage FDA to share information with the sponsors to help the advancement of PGx applications. Notably, in order to normalize practices across the industry, we suggest that the FDA provide a biannual report on the number and general details of "Required" and "Voluntary" PGx data sets received. In addition, information on biomarker status would also be required. For example: What if the FDA learns, through multiple submissions, that test results qualify for Known Valid Biomarker status; how will the FDA communicate changes to biomarker status to sponsors? Will there be new requirements imposed on the sponsors for PGx testing? Will the guidance be updated whenever a change in status has occurred or will the information be communicated using a different mechanism? A description of this information and the procedures for communicating it back to industry would be valuable.

### **Encouragement of PGx Activities**

The current Draft Guidance attends to the "data submission" aspects of PGx but does not provide guidance regarding "DNA/RNA sample collection". We believe that, it would be very constructive to include guidelines on the conditions, types of studies or study designs that would warrant DNA/RNA collection. Sample collection is the proximal portion of the PGx process and an important one. If DNA/RNA is not collected, the current Draft Guidance is ineffective. We would like to propose that the FDA consider including a section in the Guidance for PGx Data Submission on "DNA/RNA sample collection", or alternatively, a separate guidance on sample collection.

Restrictive standards on the data format and validation could discourage certain companies from submitting genomic data and possibly even discourage companies from engaging in PGx activities altogether. The standards may apply more to one platform than another and therefore may force companies to change technologies (at considerable cost) or, at least, put them at a disadvantage to companies using "FDA-approved" technologies. We feel that it would be preferable to allow for a reasonable degree of flexibility in data format and validation for PGx research activities.

### **Data Quality / Management**

Clarification on whether genomic data must be GLP-compliant if used to make decisions (e.g. inclusion/exclusion criteria) would be desirable. In general, there is currently a need to agree on quality standards for PGx testing in clinical trials. We believe that GLP is not necessary in the case of exploratory research (e.g. initial phases of toxicogenomic or global genomic studies) but should be applied in case of Pharmacogenetic testing (i.e. candidate gene based studies), particularly for those markers that are considered Known

Valid Biomarkers (*CYP2D6*, *TPMT*, etc..). Once a marker is validated or being used in clinical trial design (e.g. selection criterion for entry into a clinical trial, or for enrichment) or decision making, GLP standards should be applied whether using genetic or genomic markers. Regarding the archiving of PGx data, it is important to clarify whether data will be required to be stored in compliance with 21 CFR Part 11. This will have implications on processes for data filing.

#### **Required versus Voluntary Submission**

There is room for greater detail on Required versus Voluntary PGx data submission including clarification on the responsibility to make such decisions.

In the following sections, we would like to address some main concerns about the guidance, highlight the areas that deserve clarification and provide specific comments on specific lines in the document. Furthermore, we offer some recommendations for consideration by the FDA to ensure a more practical implementation of the Guidance on PGx Data Submission.

### **III. SPECIFIC CONCERNS ABOUT THE DRAFT GUIDANCE**

#### ***A. Pre-clinical Toxicogenomics Applications***

We believe that clarification is needed as listed below:

1. What are regulatory decisions as opposed to internal/commercial decisions?
  - ☐ The examples provided in the Guidance can be improved by dialogue between the FDA and practitioners of toxicogenomics.
  - ☐ An opinion is required on how the FDA views **any** predictive toxicology data (genomic data do not constitute a special case).
2. It is important to understand the nature of genomic or transcriptomic information:
  - ☐ Gene transcription is often at the foundation of a response to a xenobiotic and is but one part of a dynamic process.
  - ☐ In the majority of experiments the data form a starting point for further investigation and do not necessarily constitute end-points (relevant to risk assessment) in themselves.
  - ☐ Transcriptional data can give clues as to the biological processes being adversely affected by drugs, which subsequently lead to a pathological outcome. Ideally, the more proximal part of this process should be validated for risk assessment purposes to clearly show the component (e.g. protein) which is responsible for the pathology.

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- ☐ Validation of transcriptional responses is often unnecessary since they are distal to the pathology.
- 3. It is important to understand the use of genomic data in modern drug evaluation departments:
  - ☐ Much of the data are exploratory in nature:
    - Exploratory data are generated in preliminary, or predictive toxicology experiments.
    - Exploratory data are not considered to be definitive for drug safety assessment.
    - Exploratory data (together with non-genomic data) are used internally to make commercial decisions, e.g. drug selection/de-selection
    - Exploratory data may be used to decide the study design of initial GLP studies (by suggesting the additional measurement of non-routine parameters such as thyroid hormone levels) but it is the GLP study, which provides the definitive risk assessment.
    - Exploratory data may indicate similarities of lead compounds to other marketed compounds whose pre-clinical toxicity is understood and characterized.
  - ☐ Toxicogenomic approaches are very useful in understanding mechanisms of risk assessment and, on a case-by-case basis, are being used to develop hypotheses in investigative studies of toxicity:
    - In most examples, the genomic approach gives a starting point for further investigations. Differences in gene expression between treated and untreated test species indicate perturbations of biological or biochemical processes. Hypothesis-testing experiments use appropriate methods to answer questions about the perturbed biology. The genomic data in this case are not definitive and, consequently, not actually used for the assessment of risk.
    - In a small number of cases, the comparison of a transcriptional response between animal and human cells/tissues may show clear species-specific toxicity.
    - Some, but not all, genomic data gathered in investigative/mechanistic toxicity studies directly provide supportive information for drug safety. Therefore, even in these investigations, the genomic data are not entirely necessary for a drug submission. The data that prove or disprove the hypothesis are those that are required.
- 4. There is a need for open dialogue between sponsors and the FDA:
  - ☐ The toxicogenomics field is evolving and the guidelines should evolve with the increased application and understanding of the scientific approaches.
  - ☐ Frequent and open dialogue between the regulator and sponsor will help to put the guidelines into practice to the benefit of all concerned.

***B. Biomarkers: Definitions, Status Transition and Responsibilities***

There is a need for clarification and/or revision of the definitions of the three categories of data: "Known Valid Biomarker" and "Probable Valid Biomarker" and "Non-Valid Biomarker (exploratory, VGDS)". We would also appreciate a more detailed process description for transition from Probable to Known Valid Biomarker such as a process described where replication, conclusive not suggestive data, and availability for public scrutiny are all addressed. There is also a need to clarify how to submit data on combinations of biomarkers from different classes that are examined within a single study. The current guidance is unclear as to who determines biomarker status, how a biomarker becomes an established Known Valid Biomarker and how to apply existing Known Valid Biomarkers to new applications.

**Definitions**

It is crucial to clarify the definition of a Probable Valid Biomarker, among others. The definition states that, "A probable valid biomarker may not have reached the status of a Known Valid Biomarker because..." "...the data elucidating its significance, although highly suggestive, may not be conclusive" or that "...independent replication of the results may not have occurred".

Our first comment concerns the lack of replication. If an association has not been replicated, the biomarker should not be considered a Probable Valid Biomarker. It is well known that false positives are a serious problem in genetic association studies due to the large number of comparisons which are run. Therefore, we strongly suggest that a biomarker be considered "Probable" only following independent replication.

"The second comment concerns the term "highly suggestive". Could the FDA define "highly suggestive"? Does this mean that the association between a genomic biomarker and an endpoint does not need to produce a p-value of 0.05? If so, then according to their definitions a probable valid biomarker does not need to produce a significant p-value *and* the association does not need to be replicated?

**Status Transition**

Concerning the passage of a biomarker from "Probable" to "Known": will having observed the association in greater than two studies be adequate to convert a biomarker from "Probable" to "Known"? There is a large difference between how we would view a biomarker which has been repeatedly associated with an endpoint, and, say, *CYP2D6* that has been studied over many years.



Concerning the passage of a biomarker from "Non-Valid" to "Probable": If biomarkers are validated in an independent sample of patients from the same trial, would this constitute substantial evidence of "Probable Valid Biomarker"? If a prospective trial were conducted stratifying patients based on these markers, and the results were found to be significant predictors of drug response, would these markers transition to validated biomarker with the corresponding more stringent reporting requirement?

### **Responsibilities**

We would request clarification on who should determine biomarker status? Is it the sponsor, the FDA, or an external group? The responsibility for experimental validation of a biomarker, however, is best placed with the sponsor. We would like clarification on this decision-making process from the FDA.

Also, a clarification is needed on whether only approved IVD should be considered as validated biomarker, and whether a CLIA test will be evaluated as valid biomarker?

We would like to provide with the **following recommendations** associated with biomarkers:

- ❑ Validation definitions and standards should be clarified. The validation of biomarkers depends on how they will be used in drug development. Validation should be based on statistical criteria. There are existing guidance documents related to biomarkers, (e.g. April 2003 guidance including biomarker, 1998 efficacy guideline and ICH dose-response guideline) that should be used as the foundation for biomarker validation.
- ❑ Biomarker status should be evaluated on a regular basis (e.g. by reviewing VGDS) and this information communicated to industry.
- ❑ The validity of a biomarker should be addressed against clinical event severity (e.g. case of Probable Valid Biomarker, but safety issue with the drug - should data be submitted?).
- ❑ We would suggest that greater emphasis be placed on the point that the impact on reporting is dependent on how the marker is used (e.g. basing a clinical decision) and not only on biomarker status (the latter which currently seems to be over-emphasized in the Draft Guidance). Data reporting should depend on the purpose of the study, impact on clinical trial design or inclusion in the label.
- ❑ We routinely refer to the genes as being the biomarkers, yet, for DNA-based studies; it is the alleles that are the markers. Therefore, clarification would be required on the identity of the SNPs (and combinations thereof) which are considered to be "Known Valid Biomarkers" as well as the homozygous vs.

heterozygous states that also have an impact on the outcome. This adds another level of complexity that should be clarified but should not be restricting.

- There appears to be a large jump between “Probable” (where a single association is sufficient) and “Known” (where wide acceptance in the scientific community has been achieved). Perhaps there is room for an intermediate category (e.g. where an association with an endpoint has been repeatedly replicated but is not necessarily widely accepted by the scientific community).
- The guidance should consider the timing of submission of data associated with Probable Valid Biomarkers. For example, would data from cell lines, if available, suffice for an IND submission? If a drug will be used subsequently in combination chemotherapy, can the single therapy data (or data from previous indications) be used to establish biomarker status? If blood is later used as an RNA source (versus primary tissue in earlier datasets), what will be the necessary sequence of events for data submission? Given the fact that boundaries around such markers are more difficult to delineate, we suggest that submission to and acceptance by the FDA of a dataset pertaining to a Probable Valid Biomarker establishes that biomarker as valid for future submissions.
- We would appreciate a list of Known Valid Biomarkers in the Guidance and the basis on which their status has been evaluated. A list of all alleles for genes that the FDA considers as Known Valid Biomarkers and as Probable Valid Biomarkers would be very helpful. As this list will inevitably grow, possibly a database on the FDA website could achieve this as opposed to an attachment to the Guidance.
- We propose that the industry be invited to provide its own internal gene lists for what it considers to be Known Valid Biomarkers, (e.g. ADME genes) with selection criteria and body of evidence for this selection to the FDA. Publication of such markers in the scientific literature should also be encouraged. Classifying the commonly studied ADME genes in an FDA- and Industry-approved manner would be a first step in developing a list of Known Valid Biomarkers. At least with respect to the ADME genes, developing a list of Probable Valid Biomarkers would also be beneficial. Creating such lists for drug-specific or disease specific areas is perhaps not possible but the ADME biomarkers potentially impact all compounds, all disease areas, and all companies.
- We also propose that the FDA develop a committee with representation from the FDA, industry and academia to evaluate biomarker status.

- Typically biomarkers from different classifications would be examined in a single study. The submission algorithm suggests that results from different classes of biomarkers be submitted in different formats. We would propose a “Hybrid Format” report that would be divided into sections for Known, Probable and Non-Valid biomarkers.
- The use of the term “valid” for both Known and Probable classifications has already led to much confusion in discussions. Perhaps, for clarity, it would be preferable to refer to the categories as “Known Biomarker” and “Probable Biomarker” and “Non-Valid Biomarker”.

### ***C. Regulatory Submission Policies of PGx Data to FDA***

The Draft Guidance presents three decision trees to determine whether a submission is required. It is unclear when each tree would be applied. Additionally, within each category (IND, new NDA, approved NDA), the Guidance describes submission by the “usual methods”. It is unclear what this means, precisely.

The Guidance should reflect the reporting process - non sequential. There is a need to address real time issues in the IND process versus NDA phase. Therefore, it is important to be explicit regarding when PGx data submissions must be made under each regulatory stage.

#### ***C.1. Regulatory Submission of PGx Data During IND Phase***

During the IND phase, full study reports are rarely available and a requirement to submit a full study report would be burdensome. Therefore, to support a collaborative environment, providing abbreviated reports would be appreciated.

We support the use of synopses as the format for VGDS, rather than submission of full data.

#### **Microarray Data**

We propose that, for microarray data, submission of a subset of data from microarray assays should be sufficient i.e.: submission of data related to the subset of genes used to establish biological evidence and decision-making versus submission of the entire database. We feel that that submission of the entire raw data set would result in unnecessary workload to industry and FDA and that re-analysis of the dataset by different methods could potentially result in different conclusions. We feel that the raw data could be submitted on voluntary basis. A balance should be established between providing adequate data for review of the application and contributing to the process of sharing knowledge & educating the FDA, both goals of the Guidance.

In general, microarray approaches are used as an exploratory screening tool and results require validation by other technologies (protein level, RT-PCR, etc). Discussion would be required regarding whether microarray data may constitute a valid biomarker, if at all.

Collection of microarray data and tissue samples are included in GLP protocol and should be submitted. However, the report must specify that the data are exploratory.

It will be important to decide whether RNA stabilization and isolation protocols should be standardized/validated? It is well known that results can vary a great deal depending on RNA preparations.

#### **Pre-clinical data**

There is a need for consensus between FDA divisions on what it is required for submission for **non-clinical safety data** and to ensure that this is consistent with existing regulations.

The decision tree “used to support safety” requires better definition. We recommend a separate section in the Guidance, or alternatively, a separate Guidance to address pre-clinical data related to the IND phase.

### ***C.2. Regulatory Submission of PGx Data During NDA Phase***

#### **Decision Making in a Clinical Trial**

In the Guidance, a key criterion determining whether submission of pharmacogenomic data is required is whether the data are used for “decision making in a clinical trial”. A more precise definition of “decision making in a clinical trial” that would trigger a regulatory submission of PGx data is requested. The following examples illustrate the motive behind this request:

a) For example, if pharmacogenomic data were used to make decisions regarding the overall development plan of a drug without any prospective genotyping in a trial, would this be considered “decision making”? One could conceive of a scenario in which information regarding the frequency of a genotype was used to determine the size of a trial to ensure that a sufficient number of subjects with a particular genotype, without actually engaging in genotyping during the trial. Would this be considered “decision making”?

b) If the sponsor is using the test results to support scientific arguments pertaining to, for example, the safety, effectiveness, dosing and pharmacology of the drug and if there is ‘no effect’ (negative data), this would mean that data have been used to support scientific decisions thus should be submitted?



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We recommend that the sponsor should determine how the data would be used: exploratory versus supporting decision making in drug development process.

#### **Statistical Considerations**

In a clinical setting, the sample size for clinical studies will be based on the primary endpoints and, consequently, genetic data analysis may have inadequate power. This is further complicated by examination of multiple genes (in some cases, more variables than sample size) that could introduce false positive results (multiple comparison issues). Such statistical issues may render validation of biomarkers difficult. Such problems may be overcome by devoting specific studies to validation of a given marker. In our opinion, genetic data have complex statistical issues. We would welcome guidance from the FDA on this topic.

#### **Diagnostic Tests**

In pursuing diagnostic test approval, it is necessary to follow CDRH standards; early contact with CDRH as well as coordination of the development of the drug with the diagnostic test are important. If drug is developed with validated biomarker, the approval may be delayed if the test is not approved. We would like to draw the FDA attention to this critical point. There is room for input from CDHR on development of PGx diagnostic tests.

#### ***D. Voluntary Genomic Data Submission 'VGDS'***

Submission of PGx data should be viewed as an opportunity, not as a liability, to help the advancement of new technologies and their applications in development of new drugs. We endorse the FDA's approach that VGDS serves to advance science, enhance FDA education, and improve interaction with industry. We anticipate that the VGDS will allow the industry and FDA to explore possible genotype-phenotype correlations across studies and, by extension, develop a better understanding of which genes/correlations the sponsor should explore and at which stage in the development process.

However, VGDS presents some concerns to the industry, including: cost and effort, inappropriate replication of data analysis, how the data will be used, how the VGDS may be regulated, IRB delays (e.g. if informed consent might not have been obtained for VGDS), and the regulatory implications. There is an urgent need for transparency in the guidance on the **cases in which VGDS is found to have an impact on the (regulatory) decision-making process.**

FDA clearly stressed that it will not use data from VGDS for regulatory decision-making. If biomarker and data analysis is validated, a company must then submit per algorithms.

Clarification regarding the following would be helpful:

- ☐ Submission format: which is considered as “adequate” versus “desirable” for VGDS? Type of studies, type of data, e.g. summary vs. list?
- ☐ Clarification on the responsibility of sponsors to submit a full report or synopsis for VGDS: Preferred format for industry is the synopsis format.
- ☐ Who will be on the IPRG to assess the VGDS data?
- ☐ Should VGDS data go to the FDA review division and/or working group IPRG? Will Required data go to different FDA divisions? Who (at the FDA) will review what?
- ☐ ICF-related issues: A specification should be made in the guidance that the ICF should state that the “data may be submitted to regulatory authorities (such as the FDA)”.

#### ***E. Intellectual Property (IP) of VGDS***

It will be imperative for the FDA to clarify its position on intellectual property (both inventorship and ownership) if, for example, its staff recognizes novel patterns of efficacy or safety related to PGx markers in VGDSs from multiple companies.

From an intellectual property perspective, it is important for pharmaceutical companies to understand the ownership of the data voluntarily submitted and of any inventions deriving from those data in whole or part. If FDA staff, through meta-analysis of data from multiple companies, discover that a biomarker is important for safety or efficacy, who owns that invention and the right to commercialize it? Would the FDA scientist be included as an inventor? In addition, would VGDS data be subject to public review through the Freedom of Information Act? It would be reassuring to include a statement that the FDA would not seek to patent any inventions conceived or reduced to practice from the use of the submitted data.

There remains apprehension within industry surrounding IP issues for VGDS in spite of preliminary reassurance by the FDA (communicated at the DIA/FDA November 2003 meeting in Washington) that there is no need for concern since VGDS data are confidential/protected. This requires explicit representation from the agency.

#### **IV. SPECIFIC COMMENTS**

We would like also to provide comments regarding the following lines from the FDA draft guidance document:



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Lines 204-208, lines 536-540 and 563-570: We would be interested in understanding, more fully, the text in these lines and the relationship to signature profiles for SNP haplotyping or mRNAs:

Line 65-68: *"Laboratory techniques and test procedures may not be well validated. In addition, test systems may vary so that results may not be consistent"*.

This is a major point for microarray-based tests as different labs use different RNA isolation/amplification methods, labeling methods, and platforms (all of which can affect the performance and concordance across platforms). Will the FDA be able to synchronize all of the data submitted by different sponsors, given these differences, or does some level of standardization need to be considered before data submission? Most important is to recognize which test procedure gives the most viable signature(s). The best response may be on systems that utilize SNP analysis, which may be validated by various PCR procedures. Certain microarray assay results may not be validatable by independent methods or on other microarray systems but produce consistent, reproducible results that correlate with patient outcome. The internal validation based on clinical outcome and reproducibility may be the characterization that validates the gene signature.

Lines 70-71: *"The scientific framework for interpreting the physiologic, toxicologic, pharmacologic, or clinical significance of certain experimental results may not be in place"*. We propose to add ....(patho)physiologic.

Lines 121-123: *"This guidance also makes a distinction between pharmacogenomic tests that may be considered valid biomarkers appropriate for regulatory decision-making, and other tests that may be less well developed"*. The current version reads awkwardly and implies that valid biomarkers result from tests that are less well developed. The text should be revised.

Lines 139-140: What will be the statistical criteria for a "significant association" for a marker to be considered a probable biomarker? We would like more guidance on **statistical analysis** methods that will be utilized in analyzing pharmacogenomics data.

Line 172: *"In contrast, results from earlier feasibility studies done under the same IND (or outside the IND) to establish the potential usefulness of the pharmacogenomic test (e.g., from samples taken during a dose-response study) should not normally be submitted unless they provide support for the use of the test in clinical decision making"*. Clarification on "clinical decision making" is requested.

Line 229: *"The types of genetic loci or gene expression profiles being explored..."*. The FDA is expecting to learn and understand scientific issues from the voluntary data submissions in preparation for appropriately evaluating future submissions. Different test systems/techniques will qualitatively report different results. Knowing that there are differences between the gene expression profiles, test systems, and techniques being



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explored by the pharmaceutical industry, how does the FDA intend to manage differences in gene signatures between sponsors submitting data on drugs of the same class (e.g., statins in cholesterol, tyrosine kinase inhibitors in oncology, etc.)? We suggest, that at this time, that the FDA independently evaluate each sponsor's data, since independent submissions are likely to be valid under their different conditions and are not necessarily directly comparable.

Line 233: *"...and process large amounts of pharmacogenomic data streams with..."*. This may not necessarily be true if the signature discovery is performed on a 40,000 transcript, genome-wide expression profiling chip but the diagnostic (and trial data) is generated on a lower density, custom chip having only those genes involved in the signature arrayed on it. Will the FDA accept this transition with the appropriate amount of validation of the signature on the custom chip? We would propose that a custom chip (when only the relevant genes are arrayed) may provide the preferred route because it can result in an improved gene signature, with higher numbers of measurements per gene, and optimized, validated analytical performance (reproducibility, dynamic range) and assay parameters.

Line 458: *"...validation of gene expression by conventional assays such as Northern blot..."*. The list of conventional assays (Northern blot, real-time PCR, IHC, or Western blot) for validation of gene expression will probably not be possible for validation of gene expression due to the number of genes in the signature, the small magnitude of change of many of the genes, or other factors. What other methods of validation would the FDA recommend? One option would be that validation of genes in the signature via their known biological functions or pathways should also be considered.

Line 462: *"...submission of electronic file containing raw images, raw data, ..."*. We request that the FDA reexamine the need for submitting raw images, raw data, and scatter plots in light of the potential complexity of some of the gene signatures and of the data extraction algorithms. We do not agree that this amount of raw data should be needed to *"...interpret the information and independently analyze the data"* (line 431). We would suggest that normalized array intensities for those genes involved in the signature and data from clustering algorithms should be sufficient for the FDA to perform its review of pharmacogenomic data.